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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte PETER DROGE, NICOLE CHRIST and ELKE LORBACH

Appeal No. 2010-003660
Application No. 10/082,772
Technology Center 1600

Oral Hearing Held: May 12, 2011

Before DONALD E. ADAMS, LORA M. GREEN and
STEPHEN G. WALSH, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANT:

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The above-entitled matter came on for hearing on Thursday, May 12, 2011 commencing at 9:30 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Paula Lowery, Notary Public.

PROCEEDINGS

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THE USHER: Good morning. Calendar Number 35, Appeal No. 2010-003660, Mr. Highlander.

JUDGE ADAMS: Good morning, Mr. Highlander.

MR. HIGHLANDER: Good morning.

JUDGE ADAMS: We're familiar with your record. You'll have 20 minutes. You can begin when you're ready.

MR. HIGHLANDER: Good morning. My name is Steven Highlander. I represent the Appellants Droge, et al. in this appeal.

We're going to talk a little today about integrases. I'm sure you all are familiar with the technology, but I'll review briefly.

I was trying to come up with an analogy. I like analogies. I was thinking maybe an electrical cord with two male plugs at the end would be our first piece of DNA, and the target sequence would be a linear piece of DNA, perhaps with two female plugs that were joined.

When these two are brought into juxtaposition with each other under the proper conditions, with the proper enzymes, we have the male plugs attaching to female plugs and integration of the DNA.

The integrase is the enzyme that drives every action, and in certain instances it can drive the reverse reaction where the new sites that are created are now both male and female on both ends and can be brought together and the inserted DNA removed.

So the enzyme that drives this reaction, at least in part, is called integrase. I'll refer to that as INT throughout here.

There's really a fairly simple number of elements to get the minimal reaction proceeding. The integrase, the DNA that's being moved in with appropriate recombination sequences, and then a target DNA in which the integrating DNA will be received.

The present invention follows, not surprisingly, those elements pretty closely. The requirement we have in our broadest claim is that this reaction takes place inside the eukaryotic cell. The integrases that are going to drive the reaction are what are called modified integrases of the lambda family. The lambda integrase, of course is an e. coli integrase, and the integrases we're talking about here are called NH and NH218, which have some changes that allow them to have slightly different activities.

They can operate without certain factors that are sometimes present in cells, as opposed to the wild-type integrase that requires these factors.

So the Examiner has advanced five or six different references here to attack the claims. There's a rejection of the claims over two of these references, and additional references are added to address primarily dependent claims, although there's an alternative formulation of the broad rejection of YN3 claims.

The key references I think you want to talk about today are Crouzet, Christ and Droge, of which they are both inventors on this case -- but it's an earlier paper by them -- and Hartley.

Crouzet and Hartley are U.S. patents. Christ and Droge is an academic publication.

The Examiner uses Crouzet as the primary reference to reject -- again we'll talk about our main claim, Claim 29 -- and says this reference teaches

everything except NH and NH218, which are these modified integraces. I don't know if that's actually correct. I think that we've talked to the Examiner extensively about the deficiencies of Crouzet. At the time this patent was filed, it was not known that lambda, wild-type integrase, could work in eukaryotic cells.

The Examiner is sort of taking this for granted because throughout the course of Crouzet they talk about a variety of integrases, including free and flip, which are well known integrases which do work in eukaryotic cells, as well as lambda. They talk about a variety of recipient host cells.

JUDGE WALSH: Didn't the Examiner actually give an explanation of why in the Examiner's opinion the integrase was likely to work in this environment? I'm not sure I get what you're saying when you say the Examiner took it for granted. I think the Examiner gave some explanation.

MR. HIGHLANDER: About the wild-type integrase?

JUDGE WALSH: Yes, about why the integrae would work.

MR. HIGHLANDER: I think there's a reliance on the other references to draw inferences from Crouzet, but Crouzet itself -- as I said, it mentions all these things, but there's no demonstration in Crouzet.

You're right, the Examiner does argue extrapolation. The whole rejection is a series of extrapolations.

She says it's reasonable to believe from -- but there's a rejection that's only over Crouzet and Christ and Droge. There's no other evidence within Crouzet to suggest why one would believe that the lambda integrase would work in eukaryotic cells.

JUDGE GREEN: Well, they say it would work in eukaryotic cells. It's an

issued U.S. patent. We're entitled to --
MR. HIGHLANDER: Did they say lambda would work in the cells? Or do they just have a list -- in one area they have a list of cells that include free cells and prokaryotic cells. In another section they have a list of recombinases.
JUDGE GREEN: How do you think one of ordinary skill in the art would read that?
MR. HIGHLANDER: They would take the reference at face value and they would look at what the reference -- for example, the Examiner made a comment, issued patents are good for what they've enabled.
Look at the claims. There isn't a claim to lambda in eukaryotic cells. There's a claim to eukaryotic cells, but they don't mention lambda.
JUDGE ADAMS: Why would we focus ourselves solely on the claims absent the disclosure? The disclosure -- what you call an extrapolation, others may call a reasonable expectation of success.
MR. HIGHLANDER: And the only evidence we have of record on that point is Peter Droge, who has filed a declaration that says it was unknown at the time of filing whether or not the modified integrases would work in eukaryotic cells.
Now, we're still talking about lambda at this point, admittedly. So we've got a level of extrapolation to go, right?
JUDGE WALSH: Unknown in the sense of unproved or doubted?
MR. HIGHLANDER: I think questioned. It was simply not known. I mean prokaryotic cells and eukaryotic cells are very different. There's a lot of discussion about why they're different and whether that matters based on

some of these secondary references.
But the bottom line is, and I can say this with a straight face because I don't have an enabled rejection pending against me today -- patent attorneys put lots of things in patent applications.
All we know that is enabled in Crouzet is what issue --
JUDGE GREEN: Can you point to where this argument is in your Appeal Brief? I know you have the prokaryotic versus Christ and Droge working in the Crouzet reference. But where do you argue whether or not the Crouzet reference itself is enabled and whether there is doubt at the time of the filing of the Crouzet reference whether or not this would work in eukaryotic cells?
MR. HIGHLANDER: We simply just argue there's nothing in Crouzet to prove that --
JUDGE GREEN: You're talking about the modified integrases. Where do you talk about the wild-type integrase that you would have not expected from Crouzet to work?
MR. HIGHLANDER: I submit there's no proof in it that it would work.
JUDGE GREEN: Okay.
MR. HIGHLANDER: The Examiner is making the extrapolation, that's fine.
JUDGE ADAMS: Let's say the Examiner is providing a reasonable expectation of success.
MR. HIGHLANDER: For lambda.
JUDGE GREEN: For wild type, yes.
MR. HIGHLANDER: Let's assume –
JUDGE ADAMS: Let's get away from the extrapolation and use the

reasonable expectation of success language.
MR. HIGHLANDER: Okay, Crouzet, of course did not talk about modified integrases, all right? That's when we turned to Christ and Droge, which of course works in prokaryotic cells.
Dr. Droge went on the record saying looking at Christ and Droge you can't tell what those integrases are going to do in eukaryotic cells. It's as simple as that.
At that point the Examiner, I believe, has the burden to come back to us because there's evidence on the record as to belief of the inventor and the author of Christ and Droge there is no reasonable expectation of success at that point.
JUDGE GREEN: But we have a reasonable expectation that the wild type would work in eukaryotic cells.
MR. HIGHLANDER: I would not admit that on the record. I believe Crouzet has the words.
JUDGE GREEN: But that's the Examiner's argument.
MR. HIGHLANDER: That's the Examiner's argument.
JUDGE GREEN: You really haven't brought in evidence or anything to show that at the time of filing that this was wrong.
MR. HIGHLANDER: I don't believe we have to because if you look at Crouzet the reference has a bunch of words, but there's no evidence from that reference -- other than the words -- that you can take a particular embodiment from one section, which is lambda, and a particular embodiment from another section, which is eukaryotic cells, and put them together.

The Examiner is making an extrapolation.
JUDGE ADAMS: That's what the words of the patent say, right? It's not an extrapolation. It's here's a list of cells, here's a list of integrases, have at it.
MR. HIGHLANDER: Right.
JUDGE ADAMS: There is no extrapolation there. It's this and this.
MR. HIGHLANDER: We're talking about how one of ordinary skill would view that, and we've stated on the record, I believe, that there is no evidence in that reference that lambda would work in eukaryotic cells.
JUDGE WALSH: Our reviewing court has agreed that Patent Examiners can rely on disclosures and the claims of issued patents as being enabled.
JUDGE GREEN: For everything in there. Then this burden shifts to Appellant to come up with some kind of proof that that is a wrong --
MR. HIGHLANDER: That every possible embodiment, even generically described in the reference is enabled?
JUDGE WALSH: Well, I don't recall the exact language.
MR. HIGHLANDER: I don't either.
JUDGE WALSH: I think it's more like the teachings of the disclosure.
MR. HIGHLANDER: Right, and there's a lot of host cells, and a lot of integrases that are described in this reference.
Let's just assume for the rest of this argument -- we, obviously, have a bit of a disagreement here. Let's move on. Let's assume for the rest of the argument that lambda would work in eukaryotic cells.
Now, we still have to worry about the modified integrases, which is really the only -- there's only two papers that talk about modified integrases. One is Christ and Droge, which we already talked about. It's a paper it simply

looks at how these things behave in eukaryotic cells.
In fact, these integrases go back to the early '80s when they were first developed. As of Christ and Droge, and certainly as of the filing date, nobody knew if they were going to work in eukaryotic cells.
The question is can you assume from looking at Crouzet and Christ and Droge whether or not they would. I simply submit there's no evidence of record that they would.
In fact, we have the inventor's sworn declaration that it was unknown if they would. Still, actually, it's not really known why they work.
JUDGE GREEN: The declaration is an opinion declaration. He doesn't rely on evidence or bring in outside papers or anything else.
I'm not saying it's not evidence.
MR. HIGHLANDER: Right.
JUDGE GREEN: I'm just saying it's an opinion declaration.
MR. HIGHLANDER: Had he not been commenting on his own published work, I think that would maybe have a little more teeth. It is worth something, I agree with you.
But I think the fact he's commenting on his own paper, you know, the Examiner is relying on this work; and he's characterizing what his own work showed, which was prokaryotic.
So now we do have some other rejections though that combine the references. One of these relies on Capecchi, which I really don't think is relevant.
All the Examiner is using there is really -- he rejects the main claim, but also a couple of very discrete dependent claims that talk about also using

homologous sequences to tell your DNA to go before you start using the recombination, what's called site-specific recombination.

So if you look at those claims -- I forget the claim numbers offhand now -- really that's all Capecchi is relying on.

It talks about the homologous recombination, so it really doesn't get at this issue of whether or not the site-specific machinery of these mutant integrases would work.

So I don't think that's a key issue here, so I'm not going to talk any more about Capecchi.

Similarly, there's a reference called callus that's applied to some claims that talk about the reverse reaction I talked about, which is taking the extension cord back out.

Again, callus doesn't work with lambda. It works with sub-family members of the same larger family as lambda, but it doesn't work with lambda. It doesn't work with mutants, so it doesn't get back to this core issue of whether or not the mutant integrases could be understood as working in eukaryotic cells.

So what we have left are a rejection where the Examiner combines a third reference to Crouzet and Christ and Droge against Hartley; and then there's an anecdotal reference to Lang-Gustafson, which she doesn't rely on for any rejections; but we've kind of gone back and forth on what this reference might contribute to the whole picture.

Which it does deal with mutant integrases. It deals with one of them, NH.

Let's talk about Hartley for a minute. I find Hartley very, very similar to Crouzet. It's got this very broad, general discussion of a bunch of different

target cells, a bunch of different integrases, none of which are mutant. You know, talks about you can do these integration reactions.

Interestingly, some of the discussion in Hartley talks about an actual in vitro combination event followed by in vivo selection methods. So not even a cell would actually be performing the recombination reaction in a cell-free mixture.

The inventors told me that's really -- when they talk about lambda, that's what they're talking about. Again, it's all in the patent, and it's all stated there.

So to the extent you're going to take a broader view of Crouzet, one might take a broader view of Hartley. Again, it doesn't address mutant integrases. So I still don't know how we can get to the point of having a reasonable expectation of success in complicated biological systems that when you modify these integrases that they can actually work in a completely new environment which is eukaryotic cells.

Now, I can cut and run because that's all the references being cited against me; but I want to talk about Gustafson. It's on the record. I think it may have been part of the rejection at some point, but somehow it either dropped out, or it was brought as a supporting reference by us.

It talks about NH. Again, it's most like Christ and Droge in that it doesn't work in eukaryotic cells, it works in prokaryotic cells.

The Examiner has looked at this reference as trying to put some teeth into this argument you can move from a wild-type lambda to a mutant lambda assuming the wild-type lambda works in eukaryotic cells.

One of the arguments she makes is that although NH doesn't work as well on

unwound DNA, which is what you find in eukaryotic cells, as opposed to super-coiled DNA which you find in prokaryotic cells, it still works. So why wouldn't you expect that? Well, I think the fact that it works less well in its native environment suggests that we don't know that when you take an additional level of extrapolation, which is to a non-native environment, which is prokaryotic or eukaryotic cells, might you go from a reduced amount of activity to no activity.

We simply don't know.

I do want to address one comment she made. I think it first showed up in the Examiner's answer. In our Brief we have something about underwound DNA, and she questioned whether or not that was inconsistent with Dr. Droge's declaration that said that it doesn't work on relaxed DNA. You wouldn't know if it would work on relaxed DNA. Isn't underwound relaxed? I get my instructions from Germany on these, and underwound I think means -- wound is this way, and underwound is this way. So it's another way of saying negative super coiled, as opposed to unwound.

I just want to distinguish that underwound was intended to be negatively -- supercoil versus negative supercoil. So it's a little confusing.

When I read it, I thought where did that come from; and I realized that was a cut and paste from some stuff I got from Germany.

For the rest of this discussion, let's assume that Crouzet suggests that you can use lambda in eukaryotic cells. Great. We're not talking about lambda, we're talking about these mutants. They operate differently.

Christ and Droge were composed of prokaryotic cells. it doesn't comment on what would happen in eukaryotic cells.

Lang-Gustafson works in prokaryotic cells. It's the only other reference that mentions a modified INT. The rest of the references talk about perhaps what lambda would do, or don't even mention lambda at all -- Capecchi and Calos.

So in the end to have these rejections stand you have to take a leap of faith. The leap of faith is a sketchy belief that lambda should work in eukaryotic cells, even though it hasn't been proven as of the final date of either Hartley or Crouzet, would translate into mutant integrases that have somewhat different activities.

Was it possible they could work? Well, as it turns out they did. That's hindsight. At the time of filing, nobody tested this, and nobody knew whether different activities in the mutant integrases would allow them to continue working or work at all in prokaryotic cells.

JUDGE WALSH: Is there any evidence that relates the mutations of those integrases to their performance?

MR. HIGHLANDER: In prokaryotic cells?

JUDGE WALSH: No, in the context that you're claiming for this.

MR. HIGHLANDER: You know, I don't think there is. In fact, I was reviewing Dr. Droge's declaration, and it says to this day we don't really understand fully why these integrases are able to work in eukaryotic cells.

JUDGE ADAMS: Basically, what we have is a reference that says here's a whole host of cells, here's a whole host of integrases, prokaryotic cells, eukaryotic cells, have at it. Pick your choice of cell, pick your choice of integrase, go for it.

MR. HIGHLANDER: Right.

JUDGE ADAMS: Then we have a reference that says, hey, there's this new modified integrase out there. It works great in prokaryotics.

A person of ordinary skill, according to the Examiner, would say, hey, this one is just recognizing yet another integrase that can be added to this whole host of integrases listed in this original primary reference. Here's a whole host of cells, go have it. Prokaryotic, eukaryotic, what have you.

That's pretty much what this rejection is all about, right?

MR. HIGHLANDER: No. It doesn't work just great in prokaryotic cells. It has reduced activity. It was able to work without some of these additional factors, but you lose activity when you drop those out. That's clearly what Christ and Droge --

JUDGE ADAMS: But it does work, right?

MR. HIGHLANDER: It does work, however, in reduced activity.

The other issue here is one might look at these as a bunch of options. But, you know, Crouzet and Hartley had the modified integrases as prior art to them. They didn't mention them. They only mentioned Lambda.

And we have a reasonable expectation of success that's missing here, and that is -- I know I've seen many rejections that talk about biological systems perhaps less complex than these as being unpredictable in how they behave. If there's something unpredictable from prokaryotics to eukaryotics, that would fall into the category.

JUDGE ADAMS: What's the evidence to suggest unpredictability?

MR. HIGHLANDER: There's no evidence --

JUDGE ADAMS: This is a complex system? That's your unpredictability?

MR. HIGHLANDER: Well, I believe the Examiner has to come forward with more than it's possible in a complex system to make a prima facie case.

JUDGE ADAMS: Right. Anything else?

JUDGE GREEN: No.

JUDGE WALSH: No.

JUDGE ADAMS: All right. Thank you.

(Whereupon, the proceedings at 9:50 a.m. were concluded.)